CLAIMS

1. A representation of the three-dimensional solution structure of an RGS protein or portion thereof generated using the structural coordinates for RGS4-core protein.

2. The representation of claim 1 that is a representation of an RGS subfamily B protein.

3. The representation of claim 1 that is a representation of an RGS4.

4. The representation of claim 1 that is a representation of rat RGS4 .

5. The representation of claim 1 that is a representation of the Gα binding site of an RGS protein.

6. The representation of claim 1 that is a representation of the α_6-α_7 region of an RGS protein.

7. The representation of claim 1 that is a representation of the allosteric binding site in the α1-α2 region of an RGS protein.

8. The representation of claim 1 which comprises the entire core region of an RGS protein.

9. The representation of claim 1 that is generated using the structural coordinates for RGS4-core protein as determined by NMR spectroscopy.

10. A method for identifying, selecting or designing a chemical or biochemical species which is a modulator of RGS activity, RGS binding or RGS-Gα complex activity which comprised the steps:

(a) studying the interaction of one or more chemical or biochemical test species with the three-dimensional solution structure of an RGS4 protein or a portion thereof; and

(b) selecting a chemical or biochemical test species, which is predicted by its interaction with the three-dimensional structure of RGS4 to act as a modulator of an RGS protein to thereby identify, select or design the modulator.

11. The method of claim 10 wherein the modulator is identified, selected or designed based on its predicted interaction with a Gα binding site of a free RGS4 protein.

12. The method of claim 10 wherein the modulator is identified, selected or designed based on its predicted interaction with an allosteric binding site of a free RGS protein.

13. The method of claim 12 wherein the allosteric binding site is located in the α_1-α_2 region of a free RGS4 protein.

14. The method of claim 10 wherein the modulator is identified, selected or designed based on its predicted interaction with the α_6-α_7 region of a free RGS4 protein.

15. The method of claim 10 wherein the test species are selected from small organic molecules.

16. The method of claim 10 further comprising the steps of:

(a) obtaining the selected test species and

(b) assaying the test species to measure its activity as a modulator of RGS activity, RGS binding or RGS-Gα complex activity.

17. A modulator identified, selected or designed by the method of claim 10.

18. A process for identifying a substance that inhibits RGS activity, RGS binding or RGS-Gα complex activity comprising the step of determining the interaction between a candidate species and the structure of free RGS using a representation of the three-dimensional solution structure of RGS4.

19. A process for identifying a substance that mimics or promotes RGS activity, RGS binding or RGS-Gα complex activity comprising the step of determining the interaction between a candidate species and a representation of the three-dimensional structure of free RGS4.

20. A method of identifying modulators of RGS activity, RGS binding or RGS4/Gα complex activity by rational drug design comprising the steps:

(a) designing a potential modulator that will form a reversible or non-reversible bond with one or more amino acids in the RGS4 Gα binding site based upon the NMR structure coordinates of free RGS;

(b) synthesizing or otherwise obtaining the modulator; and

(c) determining whether the potential modulator inhibits or promotes the activity of RGS or RGS4/G_α complex.

21. The method of claim 20 wherein said modulator is designed to interact with one or more atoms of said one or more amino acids in the RGS4 Gα binding site and wherein said one or more amino acids is selected from the group of D117, S118 or R121.

22. The method of claim 20 wherein the amino acids are selected from S39, E41, N42, L113, D117, S118, R121 or N82

23. A method for identifying modulators of RGS activity, RGS binding or RGS4/Gα complex activity by rational drug design comprising the steps:

(a) designing a potential modulator that will form a reversible or non-reversible bond with one or more amino acids in the allosteric binding site in the α1-α2 region of RGS based upon the NMR structure coordinates of free RGS4;

(b) synthesizing or otherwise obtaining the modulator; and

(c) determining whether the potential modulator inhibits or promotes the activity of RGS or RGS4/G_α complex.

24. The method of claim 23 wherein said modulator is designed to interact with one or more atoms of said one or more amino acids in the allosteric binding site and wherein said one or more atoms is selected from the group of RGS residues V10, W13, L17, I20, H23, E24, C25 and T132.

25. A modulator identified by the method of claim 23.

26. A method of identifying modulators of RGS activity, RGS binding or RGS4/Gα complex activity by rational drug design comprising the steps:

(a) designing a potential modulator that will form a reversible or non-reversible bond with one or more amino acids in the α_6-α_7 region of RGS4;

(b) synthesizing or otherwise obtaining the modulator; and

(c) determining whether the potential modulator inhibits or promotes the activity of RGS or RGS4-G_α complex.

27. The method of claim 26 wherein the modulator activity is assesses using an enzyme assay.

28. A method for identifying a potential modulator of RGS activity, RGS binding or RGS-Gα complex activity by rational drug design comprising the steps:

30. The method of claim 28 wherein the three dimensional structure of step (a) is that of free RGS4 as defined by the relative structural coordinates of RGS4-core protein according to Table 2, ± a root mean square deviation of not more than 1.5Å from the conserved backbone atoms of the amino acids of RGS4-core.

31. A modulator identified by the method of claim 28.

32. The method of claim 28 wherein the three dimensional structure of step (a) is that of an RGS protein other than RGS4 and wherein the three dimensional structure of the RGS protein other than RGS4 is obtained by molecular replacement analysis or homology modeling techniques employing the relative structural coordinates of RGS4-core protein according to Table 2, ± a root mean square deviation of not more than 1.5Å from the conserved backbone atoms of the amino acids of RGS4-core.

33. The method of claim 32 wherein the RGS protein other than RGS4 is an RGS subfamily B protein.

34. The method of claim 28 wherein the step of employing the three dimensional structure to designing or select the potential inhibitor comprises the steps of:

(1) identifying chemical or biochemical species or fragments thereof capable of binding to an RGS4 protein; and

(2) assembling the identified chemical entities or fragments into a single molecule to provide the structure of a potential inhibitor.

35. The method of claim 34 wherein in step (a) the chemical or biochemical species or fragments thereof capable of binding to the Gα binding site of a free RGS-core is a protein.

36. The method of claim 34 wherein in step (a) the chemical or biochemical species or fragments thereof capable of binding to the allosteric binding site in the α_1-α_2 region of a free RGS core protein are identified.

37. The method of claim 34 wherein in step (a) the chemical or biochemical species or fragments thereof capable of binding to α_6-α_7 region of a free RGS core protein are identified.

38. The method of claim 34 further comprising the step of testing the potential inhibitor designed or selected in step (b) as an modulator of an RGS protein.

39. A modulator identified by the method of claim 34.

40. A method for identifying a mutant of RGS4 where the biological activity of the derivative is different from that of RGS4 comprising the steps of:

(a) identifying amino acid residues of RGS4 protein that are involved in the function of the protein for regulation of G-protein signaling from the three dimensional structure of free RGS4;

(b) modifying one or more of the RGS4 amino acid residues identified in step (a) to generate the derivative of RGS4.

41. The method of claim 40 wherein the amino acid residues of RGS4 are modified by site directed mutagenesis of an RGS4 coding sequences after which the derivative RGS4 protein is expressed from the mutagenized RGS4 coding sequence.

42. The method of claim 40 wherein the amino acids modified are in the Gα binding site of RGS4.

43. The method of claim 40 wherein the amino acids modified are in an allosteric binding site of RGS4.

44. The method of claim 40 wherein the amino acids modified are in the α_6-α_7 region of RGS4.

45. A method for identifying potential modulators of an RGS protein which comprises the steps of:

(a) identifying an RGS binding site by detecting perturbations of the NMR resonances in NMR spectra of RGS4 core protein in the presence and absence of chemical and biochemcial species that potential bind to RGS4;

(b) employing the three dimensional structure of free RGS4 at the binding site identified in step (b) to select or design chemical or biochemical species that are predicted to bind at the binding site;

(c) testing the chemical or biochemical species that are predicted to bind at the binding site for function as an modulator of RGS activity or RGS-Gα complex activity.